Original Article – Clinical Science

Ten-year reinvestigation of ocular manifestations in Marfan syndrome

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Abstract

Importance: Long term follow-up of Marfan syndrome (MFS) patients

Background: Investigate changes in ocular features in Marfan syndrome patients fulfilling the Ghent-2 criteria following a period of 10 years.

Design: Repeated cross-sectional study with two observations.

Participants: 84 MFS patients were investigated in 2003-2004 (baseline). Forty-four of these patients (52%) were examined after 10 years

Methods: A comprehensive ocular examination performed at baseline and follow-up.

Main Outcome measures: Development or progression of ectopia lentis (EL).

Results*:* At follow-up, mean age was 50.1±11.9 years (range, 30-80 years), 74% were female, and 70% of the patients were diagnosed with EL compared to 66% at baseline. Two patients (3 eyes) had developed EL over the decade, representing a 13% risk. Furthermore, 1 eye had progressed from a subtle tilt of the lens to dislocation. We found no significant change in the axial length ($p = 0.96$), the corneal curvature ($p = 0.64$), or the spherical equivalent ($p = 0.23$. Best corrected visual acuity was improved at follow-up ($p = 0.02$). There were 7% and 33% risks for development of retinal detachment and cataract between baseline and follow-up, respectively.

Conclusions and Relevance: Our study indicates that even though EL typically occurs at an early stage in most MFS patients, there is still a risk of developing EL in adulthood. The risk of developing vision-threatening complications such as retinal detachment and cataract was much higher than in

the normal population, but even so, the visual potential of the MFS patients was relatively good.

Keywords: Marfan syndrome, ectopia lentis, axial length, corneal curvature, visual acuity.

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder affecting most typically the cardiovascular, ocular, and skeletal systems. Reports on the prevalence of MFS give varying numbers, from 4.6 to 6.5 per 100 000.[1-3] MFS is caused by mutations in the gene encoding for the connective tissue protein, Fibrillin-1(*FBN1*), but presumed disease-causing variants in *FBN1* have been found in a number of different disorders.[4,5] Thus, the diagnosis of MFS is based on diagnostic criteria. Börger first described ectopia lentis (EL) as part of MFS in 1914.[6] In 1996, De Paepe et al. presented a set of criteria based on clinical findings based in various organ systems, *FBN1* mutations, and family history called the Ghent nosology (Ghent-1).[1] EL is a major criterion based on this nosology. Other ocular features included as minor criteria are abnormally flat cornea, increased axial length (AL) of the globe, and hypoplastic iris or hypoplastic ciliary body.

Although Ghent-1 has a high specificity to identify MFS patients, its sensitivity was questioned as some of the physiological features were not sufficiently validated. Therefore, an expert panel presented a revised Ghent nosology (Ghent-2) in 2010.[7] Ghent-2 has aortic root aneurysm/dissection and EL as cardinal features. Other than EL, myopia > 3 diopters (D) is the only ocular feature included. Other ocular conditions that have been suggested as being related to MFS, but not included in the Ghent criteria, are increased risk of retinal detachment, early cataract, keratoconus, and glaucoma.[1,8-10]

There are several reports on the ocular characteristics of MFS patients,[10-12] but we are not aware of any studies that report changes in ocular findings over a long period of time in patients who are diagnosed with MFS using the current diagnostic criteria. In a previous study we presented our findings after a comprehensive ocular examination in adults diagnosed with MFS based on the Ghent-1 criteria.[13] The aim of the present study is to investigate the changes in ocular features in these same patients after 10 years. However, for this study, we only included patients who meet the Ghent-2 criteria for the MFS diagnosis.

Methods:

Design and ethics:

This is a repeated cross-sectional study, where data were collected twice, in 2003 – 2004 (baseline) and 2014 – 2015 (follow-up). The patients went through a comprehensive interdisciplinary examination of all relevant organ systems both at baseline and follow-up.

Research approval from the Regional Committees for Medical and Health Research Ethics was obtained (number: 2013/2109). Written informed consent was obtained from all study subjects.

Subjects

The original study population consisted of 105 individuals with presumed MFS, and 87 patients were found to fulfil the Ghent-1 criteria.[14-20] We have previously presented the ocular findings of these 87 patients.[13]

Since baseline, new methods for sequencing genetic analysis have been available, and after rescoring the results from the baseline examinations, 84 of the 105 participants were found to fulfil Ghent-1. Sixteen of these 84 were deceased after 10 years. Of the 68 survivors, 45 were enrolled in the follow-up. In the present study, those patients who fulfilled the Ghent-2 criteria at follow-up were included and compared to their findings at baseline. One of the 45 patients was found not to fulfil the Ghent-2 criteria and was excluded from the study.

Thus, the reinvestigation included 44 patients (52%), of whom 42 were FBN1 positive.

Eye examination

All subjects had a comprehensive ocular examination performed by an experienced optometrist and ophthalmologist. To ensure optimal comparisons, all devices, except for the visual acuity chart, were applied as at baseline.

Best corrected visual acuity (BCVA) was measured with ClearChart (ClearChart® 2 Digital Acuity System, Reichert Business Unit, Munich, Germany) and measured and expressed as the logarithm of the minimal angle of resolution (logMAR). The visual acuity chart applied at baseline was an Early Treatment Diabetic Retinopathy Study (ETDRS) standardized viewer (Lighthouse International, New York, NY). Spherical equivalent (SE) was calculated and noted in D. For evaluation of corneal topography, Pentacam (Oculus Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany) was used. Keratoconus was evaluated by evaluating the corneal curvature, thickness, anterior and posterior elevation, and the distribution pattern of each of these elements [21,22] Visual impairment was defined according to the International Classification of Diseases – 10 (ICD-10) from the World Health Organization (WHO). Patients with binocular BCVA of Category 1 or more were defined as visually impaired (Snellen < 0.3 or logMAR > 0.5).

Intraocular pressure (IOP) was measured with Goldmann applanation tonometry. Keratometry (K) was measured with auto refractor (Automatic Refractor Model 597, Humphrey-Zeiss, Carl Zeiss Meditec AG, Jena, Germany). The Kmean was calculated as the mean value of K1 and K2 and noted in D. The AL and central corneal thickness (CCT) were measured by A-scan ultrasound (Tomey AL-1000, Tomey Corporation, Nagoya, Japan).

EL was evaluated after complete pupillary dilatation (cyclopentolate 10 mg/ml and phenylephrine 100 mg/ml); the patients were asked to look in all directions for evaluation of any dislocation. We classified the EL as following: grade 0 = no EL; grade 1 = EL with the lens subluxated (only a subtle posterior tilt, often with a corresponding iridodonesis); grade 2 = EL with luxated lens (the lens had any vertical or horizontal displacement, most commonly superotemporal). For ocular history before and between the two examinations, we reviewed the patients' medical records and noted if EL was described prior to cataract surgery in pseudophakic and aphakic patients. When analysing change in the prevalence of EL and retinal detachment, both eyes were included. For analysis of BCVA, SE, K, CCT, AL, and IOP only the right eyes were included to avoid any correlation between the two eyes in the interpretation of the data. We also estimated the risk for developing EL, cataract, and retinal detachment in either one or both eyes over the 10-year period.

Statistics:

Continuous data was assessed for normality to clarify for *t* test suitability. To compare the categorical and continuous data between the baseline and follow-up examinations, we used the McNemar test for paired data and the paired sample *t* test, respectively. Chi-square test was used when comparing categorical data for two groups. The statistical analysis was conducted using IBM SPSS version 22.0 (IBM SPSS Statistics, Armonk, New York, USA), and $P < 0.05$ was considered statistically significant.

Results:

Mean age of the patients at the follow-up examination was 50.1±11.9 years (range, 30-80 years) and 33 of the 44 patients were women (74%). One right eye was prosthetic and was excluded from all analyses except for prevalence of EL and retinal detachment.

Ectopia lentis

At follow-up, 31 patients (70%) were found to have EL. As shown in Tables 1 and 2, 2 patients (3 eyes) developed EL from baseline. This means that 2 out of the 15 patients with no EL at baseline developed this condition, representing a 13% risk over the decade. EL was noted in both eyes of a 47 years old patient and in the left eye of a patient 34 years of age. Both patients had subluxations with no need for surgery. In addition, 1 patient had progression from a subtle tilt (Grade 1) to superotemporal dislocation (Grade 2) in one eye from baseline to follow-up, which required clear lens extraction with implantation of a Cionni modified capsular tension ring (Morcher Gmbh, Stuttgart, Germany) and a posterior chamber IOL at the age of 27. Of the 51 (61%) patents with EL at baseline, 29 (57%) patients were examined at follow-up. In contrast, of the original 33 patients without EL at baseline, 15 patients (45%) were included in the follow-up examination (p=0.31).

At baseline 12 patients (21 eyes) had had clear lens extraction with implantation of a Cionni modified capsular tension ring. During the ten year period an additional of 6 patients (10 eyes) had such surgery.

Table 1: Number of eyes with ectopia lentis at baseline and follow-up. Marked in cursive is the number of eyes that had developed ectopia lentis or progression in type of ectopia lentis. N=88 eyes.

		Follow-up		
		No EL	**Subluxation**	**Luxation**
Baseline	**No EL**	29	*3*	0
	Subluxation		19	*1*
	Luxation			36

EL = ectopia lentis

Table 2: Type of lens status in eyes with ectopia lentis and no ectopia lentis at the two examinations, N=88 eyes/44 patients

	Ectopia lentis			
	Baseline		**Follow-up**	
	EL (eyes (%))	**No EL (eyes (%))**	**EL (eyes (%))**	**No EL (eyes (%))**
Phakic	34 (39)	32 (36)	21 (24)	25 (27)
Pseudophakic	4 (5)	0	22 (25)	4 (5)
Aphakic	18 (20)	0	16 (18)	0
Total (100 %)	56 (64)	32 (36)	59 (67)	29 (32)
	(29 patients, 66%)	(15 patients, 34%)[†]	(31 patients, 70%)	(13 patients, 30%)[‡]

EL = ectopia lentis

[†] Two patients had EL only in one eye and are therefore categorized as patients with EL

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Cataract:

Fourteen patients (32%) had cataract or were pseudophakic at baseline. Ten patients (33%) developed cataract in one or both eyes during the 10 years. Of these, 6 patients (20%) had cataract without surgery (1 patient also presented with EL), 1 patient (3%) had undergone surgery for cataract, and 3 patients (10%) had undergone surgery for combined cataract and EL. This means that of the 10 patients with cataract development; 4 patients (13%) and 6 patients (20%) were diagnosed with and without EL, respectively (p = 0.25).

Ocular biometric characteristics:

Table 3 shows the distribution of biometric data in right eyes at both examinations. There were significant changes in BCVA, and IOP from baseline to follow-up, whereas there were no significant changes in the frequency of eyes with myopia exceeding 3 D; 9 (41%) vs 10 eyes (45%) (p = 1.00), or a Kmean of 41.5D or below; 23 (56%) and 24 eyes (59%) at baseline and follow-up, respectively (p = 1.00). Of the eyes with AL longer than 24.5mm, there were 22 (56%) and 21 eyes (54%) at baseline and follow-up, respectively (p = 1.00). No patients had undergone refractive surgery at baseline or follow-up. There were no cases of keratoconus.

Table 3: Ocular biometric characteristics (right eye) at baseline and follow-up expressed as mean, standard deviation (SD), and range.

Variables (n)	Baseline Mean ± SD (range)	Follow-up Mean ± SD (range)	*P* Value*	Exclusion criteria
AL (mm) (39)	25.29 ± 3.14 (20.28 - 37.80)	25.29 ± 3.31 (20.15 - 37.81)	0.96	Previous surgery for RD
K (D) (41)	41.48 ± 1.84 (37.63 - 46.50)	41.44 ± 1.70 (38.38 - 45.75)	0.64	
CCT (µm) (42)	548 ± 40.54 (473 - 648)	548 ± 37.45 (489 - 645)	0.97	
SE (D) (22)	-4.20 ± 7.26 (-28.00 - 2.13)	-3.89 ± 7.45 (-28.00 - 4.00)	0.23	Previous lens surgery
BCVA (39)	0.18 ± 0.46 (-0.24 - 2.50)	0.12 ± 0.47 (-0.24 - 2.50)	0.02	Amblyopia
IOP (mmHg) (43)	12.5 ± 2.72 (8 - 18)	13.5 ± 2.98 (8-24)	0.02	

AL=axial length, K=keratometry, D = diopter, CCT=central corneal thickness, SE=spherical equivalent, BCVA=best corrected visual acuity expressed in logMAR, IOP=intraocular pressure, RD=retinal detachment

**P* Value for changes from baseline to follow-up (paired t-test)

At the baseline examination there were 4 patients (9%) with binocular visual impairment of WHO's Category 1 or worse. One of these 4 patients saw an

improvement to 0.34 logMAR at follow-up and was no longer categorized as visually impaired. This patient had undergone clear lens extraction for EL with posterior chamber IOL and Cionni ring between the two examinations. Over the decade, 7 patients (16%) had improvement and 2 patients (5%) had a worsening of visual acuity of more than two lines (Table 4).

Table 4: Patients with change in best corrected visual acuity in right eye of more than two lines.

Patient no.	BCVA baseline logMAR	BCVA follow-up logMAR	Change in BCVA	EL	Causes of change in BCVA
1	0,66	0,2	Improved	No	Contact lens with improved design and material
2	0,3	-0,04	Improved	Yes	Cataract surgery with IOL and Cionni ring
3	0,54	0,24	Improved	No	Contact lens with improved design and material
4	0,26	-0,04	Improved	Yes	Cataract surgery without IOL implantation
5	0,32	0,06	Improved	Yes	Cataract surgery with IOL and Cionni ring
6	0,16	-0,04	Improved	No	Cataract surgery with IOL
7	0,54	0,34	Improved	Yes	Cataract surgery with IOL and Cionni ring
8	0,88	1,2	Reduced	Yes	Excessive myopia with degenerative changes in fundus
9	-0,02	0,2	Reduced	No	Cataract

EL= ectopia lentis, BCVA = best corrected visual acuity, expressed in logMAR and Snellen, IOL= intraocular lens

Retinal detachment and glaucoma

Three patients (4 eyes) had previously been treated for retinal detachment at baseline. During the 10 years, an additional 3 patients (4 eyes) had undergone surgery for this condition. This represents a risk for developing retinal detachment over the 10-year period of 7%. EL was present in 3 of the 4 eyes that had retinal detachment from baseline to follow-up. The one eye without EL was excessive myopic (-13D). One eye developed retinal detachment after

clear lens extraction. The other 3 cases had no preceding surgery. In total, 8 eyes (9%) had undergone surgery for retinal detachment prior to follow-up. Only one patient (2%) had glaucoma (in both eyes) at the baseline examination. No new cases of glaucoma were noted at follow-up.

Discussion:

To the best of our knowledge, the current study is the first to present changes in ocular features over a long-time period in adults with verified MFS based on the Ghent-2 criteria. We found a 13% risk of developing EL over a period of 10 years, and further identified the progression of 1 eye from a subtle tilt posteriorly to a superotemporal dislocation. Maumenee's study from 1981 is the only previous publication presenting a long-time follow-up of ocular features in MFS.[11] At that time, the diagnosis was based on clinical findings without genetic testing. Of the 53 patients examined more than once, there was a change in lens position in 13% of the patients. Although Maumenee did not have the same criteria for diagnosing MFS as our group, she found about the same risk of progression as the present study of adult MFS patients.

There is reason to believe that EL may be present from birth in some MFS patients. One study found EL in 38% of neonates and another study reported that MFS was diagnosed in patients at zero age, but did not specify if EL was present at birth.[2,23] Other studies have not found EL before the age of 18 months.[24,25] Studies in different age groups have reported a frequency of EL in children younger than 10 years from 63% to 75% and younger than 17 years from 15% to 57%.[11,12,23,24,26,27] Independent of age, the prevalence of EL is reported to be between 30% and 87% and indicate that there might be progression of EL after childhood, even though it seems that most dislocations develop before 18 years of age.[9-11,13,28-32] However, there are limited studies estimating at what time the EL occurs and at what age does the risk of

progression become insignificant. In the present study, we found 4 patients with development or progression of EL during the ten years, and the oldest of these patients was 37 years old at baseline. Therefore, our study highlights the importance of regular examinations of the lens status even in adult MFS patients to reveal EL or the progression of EL.

According to the Ghent-2 criteria, myopia greater than 3D and EL are the only ocular criteria for diagnosing MFS. Our study found no change in the frequency of myopia exceeding 3D and mean SE between baseline and follow-up. These findings correlate with other studies reporting myopia exceeding 3D in patients with MFS, indicating that myopia tends to be stable over time in adult MFS patients.[10,11,13,32,33]

Since increased AL will induce myopia and flattened cornea will decrease this effect, the SE will depend on their mutual effects. In the current study, there were no significant changes in AL or K from baseline to follow-up and no changes in the frequency of MFS patients with AL over 24.5mm or K values flatter than 41.5D. This corresponds to studies on healthy adults where AL seems to be stable or decrease and K seems to be stable.[34,35] One study found longer AL in the adult MFS patients compared to in the children, but no difference in K values.[12] One hypothesis behind longer AL in MFS is that the altered fibrillin molecule may allow for stretching of the sclera and thereby the globe over time.[36] According to this hypothesis, one may also speculate that abnormalities in the elastic components of the corneal stroma results in corneal

thinning.[36,37] Most studies indicate a decreased CCT in MFS.[9,30-32] We found no indication of further thinning of the cornea over the years in adult MFS patients. This correlates with studies on healthy individuals which have shown that there is either a small decrease or no change in CCT over time.[38,39] This means that our study cannot support the hypothesis that a weakening of the ocular tissue due to altered fibrillin molecules may result in enlarging the globe and/or thinning of the cornea over a long period of time.

Due to the changes in elastic fibers in MFS, there has also been a belief that there is a higher risk of keratoconus in these patients.[37] However, we have not found any studies reporting a higher range of keratoconus in MFS patients.[9,11,31] Neither did we notice any patients with keratoconus in our study. As the reported prevalence of keratoconus is reported to be as low as 265 per 100 000 individuals,[40] the sample size of our study is, of course, far too small for estimating the risk of keratoconus in MFS. However, we still question whether there is a real increased risk of keratoconus, and further studies are needed to answer this question.

The mean visual acuity improved during the 10 years, even though 3 patients had been treated for retinal detachment. However, 5 patients had undergone cataract surgery and modern contact lens materials and design also had a positive impact on the visual outcome in some patients. These results may indicate that adult MFS patients have an encouraging visual prognosis over a long period of time. Still, a mean logMAR of 0.12, indicates that patients with

MFS should be informed that their visual prognosis is not as good as it is for the general population.[29,32]

Retinal detachment is a severe vision-threatening complication. It is reported to occur in 4% to 15% of patients with MFS.[10,28,32,41] In our study, the risk of developing retinal detachment over the 10 years was about 7%.This illustrates that the increased risk for retinal detachment in MFS patients is substantial.

Cataract is known to occur earlier in MFS patients.[1,32,42] This was also the case in our study, and we found a 33% risk for developing cataracts during the 10-year period. There was no significant difference in patients with or without EL in this respect, which may indicate that EL may not have an impact on the development of cataracts in these patients.

We found a small increase in IOP over the 10 years. Different studies have reported an association between MFS and increased IOP.[1,29,42] However, we have not been able to find any studies that confirm this statement. In our sample, there was only one patient with glaucoma and we agree with reports suggesting that glaucoma among MFS patients needs further evaluation.[1,11,32]

A limitation to the present study is that data for the time frame between the two examinations was collected from medical records and that different examiners were involved in the two examinations. However, the examination techniques were carefully described, the same equipment was used and we gathered all

available information from medical records during the 10 years. Further, we cannot rule out that EL was overlooked. However, for both our baseline and follow-up examinations, an experienced ophthalmologist examined the patients and was especially focused on looking for EL with the pupils fully dilated. Of course, there may also be a possibility that a subtle increase in the posterior tilt or a further dislocation occurred between the two study examinations. Thus, the risk of a minor progression in EL in adulthood may be higher than described in the present study. Because of the nature of MFS as a rare disorder, the number of patients available to study is limited. This will influence the strength of our results. There were, a relatively large proportion of the patients from the original study who did not participate in the re-examination, and there tended to be a smaller proportion of patients with EL in the drop out group. However, this difference was not statistically significant. On the other hand, the patients who were deceased or too ill to participate in the follow-up study, might represent the most advanced stages of MFS with a potentially higher rate of EL and other ocular pathologies than the participants in the study. In contrast, there is also a possibility that patients who had no ocular symptoms did not feel the need for participating in the follow-up examination. The strength of our study is the follow-up of 10 years and a cohort of verified MFS patients. Furthermore, all patients underwent genetic testing and a comprehensive investigation including all relevant organ systems by a multidisciplinary investigation group.

In summary, our study represents the first long-term follow-up of ocular findings in adults with verified MFS. Our results revealed a risk of developing EL or

progression of EL even in adult MFS and a high occurrence of retinal detachment and cataract formation. All of these findings lead us to emphasize the importance of regular visits to an ophthalmologist for this patient group. In spite of the increased risk of these vision-threatening conditions, there was generally a good visual prognosis over time.

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